April 3, 2003

F.J. Sonny Maher
HQPD Panel Manager
The American Chemistry Council Hydroquinone Precursors
and Derivatives Panel DIPD Task Force
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Maher:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Diisopropylbenzene Category posted on the ChemRTK HPV Challenge Program Web site on December 4, 2002. I commend The American Chemistry Council's Hydroquinone Precursors and Derivatives Panel DIPD Task Force for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The American Chemistry Council Hydroquinone Precursors and Derivatives Panel DIPD Task Force advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Diisopropylbenzene Category

SUMMARY OF EPA COMMENTS

The sponsor, the Hydroquinone Precursors and Derivatives Panel DIPB Task Force of the American Chemistry Council, submitted a test plan and robust summaries to EPA for diisopropylbenzenes dated November 14, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 4, 2002. The category consists of *m*-diisopropylbenzene (CAS No. 99-62-7), *p*-diisopropylbenzene (CAS No. 100-18-5), and mixed diisopropylbenzene isomers (CAS No. 25321-09-9).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals in this category is adequate.

2. Substance Definition. The submitter indicates that diisopropylbenzene (CAS No 25321-09-9) consists of a variable composition of ortho, meta, and para isomers. The submitter needs to provide ranges of typical percentage of each isomer in the mixture.

3. Physicochemical Properties. The data provided by the submitter for boiling point and vapor pressure are adequate for the purposes of the HPV Challenge Program. The submitter needs to correct some inconsistencies in the test plan, robust summaries, and references.

4. Environmental Fate. The data provided for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. The data for stability in water on the analog 1,4-diethylbenzene are adequate for the purposes of the HPV Challenge Program, but the submitter needs to augment the robust summary. The submitter needs to provide a robust summary with biodegradation data for *m*-diisopropylbenzene or for its analogue, and a technical discussion on the relative importance of *o*-diisopropylbenzene in the isomer mixture and its biodegradation potential.

5. Health Effects. EPA agrees with the submitter's Test Plan for meeting the health effects endpoints with the exception of chromosomal aberrations, reproductive, and developmental toxicity endpoints. EPA reserves judgment on the chromosomal aberrations endpoint pending receipt of additional information on cytotoxicity. EPA, however, tentatively accepts that no additional test data are needed for reproductive and developmental endpoints pending receipt of adequate robust summaries.

6. Ecological Effects. EPA considers the submitted acute data for fish and aquatic invertebrates inadequate for the purposes of the HPV Challenge Program. For algae, EPA reserves judgement on data adequacy pending submission of analog and SAR data in robust summary format.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE DIISOPROPYLBENZENE CHALLENGE SUBMISSION

Category Definition

The submitter proposed a category to cover three substances consisting of *m*-diisopropylbenzene, *p*-diisopropylbenzene, and mixed diisopropylbenzene isomers. The first two members of the category contain >95% and >99% of their respective isomers, with other diisopropylbenzene isomers also present as minor components. The mixed diisopropylbenzenes contain variable proportions of the ortho, meta,

and para diisopropylbenzene isomers. The submitter needs to provide typical ranges of isomeric composition, to the extent possible.

Category Justification

The submitter adequately supports grouping the chemicals in the diisopropylbenzene category on the basis of their structural, physicochemical, environmental fate, and toxicological property similarities. Measured and estimated properties for the individual and mixed isomers support this grouping for the majority of the SIDS-level endpoints. The use of alkylbenzenes (cumene, ethylbenzene, diethylbenzene) as analogs for some SIDS-level endpoints is also supported adequately by the data and other evidence describing the physicochemical and/or metabolic similarities between these representative chemicals and the diisopropylbenzenes.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitter needs to specify the exact source for each value reported in table 1 (page 8) and indicate whether the value is measured or estimated.

The data provided by the submitter for boiling point and vapor pressure are adequate for the purposes of the HPV Challenge Program.

Melting point. The data provided by the submitter for *m*-diisopropylbenzene, and *p*-diisopropylbenzene are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide the melting point data for the mixed isomer (CAS No. 25321-09-9) that were indicated as available on page 9 of the test plan in robust summary format.

Vapor pressure. The submitter needs to check its vapor pressure reference for the isomeric mixture (CAS No. 25321-09-9).

Partition coefficient. In table 1 (page 8), the submitter reports log K_{ow} values of 4.9, 5.4, and 5.71 for diisopropylbenzene, *m*-diisopropylbenzene, and *p*-diisopropylbenzene, respectively (obtained from HSDB, estimation models and MSDS sheets), whereas on pages 20-21, it reports log K_{ow} values of 4.9, 4.9, and 3.45, respectively (estimated using KOWIN). The submitter needs to address this inconsistency.

Water solubility. In table 1 (page 8), the submitter reports a water solubility value of 1 ppm for the mixed isomers (CAS No. 25321-09-9), whereas on page 22, it reports a value of 4.325 (obtained from EPIWIN). The submitter needs to address this inconsistency.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter needs to add to the robust summary the information that diisopropylbenzene category members do not have functional groups that are susceptible to hydrolysis.

Biodegradation. On page 9 of the test plan, the submitter indicates that for *m*-diisopropylbenzene the endpoint is satisfied by using data from a structurally similar chemical. However, the submitter did not provide a robust summary with this information. The submitter needs to provide a robust summary with

biodegradation data for *m*-diisopropylbenzene or its analogue. The submitter also needs to provide a technical discussion on the relative importance of *o*-diisopropylbenzene in the isomer mixture and its biodegradation potential.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data were submitted for the acute toxicity, repeated-dose toxicity, and gene mutation endpoints for purposes of the HPV Challenge Program. EPA also tentatively accepts that no additional test data are needed for reproductive and developmental endpoints, pending receipt of adequate robust summaries. However, the robust summary for the chromosomal aberrations endpoint for diisopropylbenzene lacked sufficient detail to fully evaluate the study.

Genetic Toxicity (chromosomal endpoint). EPA considers studies conducted using a mixture having a minor proportion of diisopropylbenzene (historically 25-40%) inadequate because the exact composition of the tested material is unknown and most of the mixture is undefined. For the *in vitro* chromosomal aberrations test, EPA reserves judgment on its adequacy pending submission of information on the cytotoxic concentration and/or the reason for selecting the dose levels used in the study.

Reproductive Toxicity. The submitter needs to provide robust summaries for studies on analogs that are described in Appendix 1 and the two studies by Elisuiskaya (1970a,b). EPA was able to retrieve an abstract on one of these studies (TOXLINE, Secondary SourceID:HEEP/72/02289). Although it may not contain core data that would be requested by OECD Guidelines, the rat study provides important evidence of the potential reproductive toxicity of diisopropylbenzene. Effects reported in the abstract include disturbed estrus cycles, decreased capacity for conception, decreased number of offspring, and decreased offspring weight (Elisuiskaya, 1970a). The analog data discussed in the literature review report did not show the reproductive effects, whereas the sponsored chemical did.

Developmental Toxicity. The submitter needs to provide robust summaries for studies on analogs that are described in Appendix 1.

Ecological Effects (fish, invertebrates, and algae).

The submitted acute toxicity data for fish and invertebrates are inadequate. For fish and invertebrates, each test was conducted at one test concentration only and either below the water solubility limit of the test substance using the measured concentrations or at the water solubility limit of the test substance using the nominal concentrations. Therefore, the results were insufficient to determine the toxicity of the test substances. For algae, the submitter did not provide the analog data in robust summary format or the input values for the SAR data submitted. EPA reserves judgement on the adequacy of the algal data pending submission of analog and SAR data in robust summary format.

EPA suggests that the submitter conduct a chronic daphnia test instead of acute tests because the log Kow values for these chemicals are greater than 4.2.

Specific Comments on the Robust Summaries

Generic comments

The following comments apply to all of the robust summaries provided by the submitter. The submitter needs to confirm that internet hyperlinks are correct. Each summary should clearly identify the component percentages in test mixtures for each chemical or class. Studies that tested mixtures that were undefined or contained only a minor fraction of diisopropylbenzene are not acceptable for the purposes of the HPV Challenge Program.

Physicochemical Properties

Vapor pressure. The submitter's 0.25-0.39 mm Hg value for the isomeric mixture could not be found in the Lide reference quoted on page 19 of the robust summaries. The submitter needs to check this reference.

Health Effects

A robust summary for a chromosomal aberration assay in cultured Chinese hamster lung cells omitted the number of replicates and information on cytotoxic doses.

Ecological Effects

Algae. The submitter needs to provide the analog data in robust summary format and input values for SAR data.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.